8EHQ-0295-13324

8EHQ-95-13324

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(A)

February 6, 1995

CERTIFIED MAIL
RETURN RECEIPT REQUESTED
P 253 155 589

COMPANY SANITIZED

OPPT Document Processing Center (7407)
ATTN: Section 8(e) Coordinator
Office of Pollution Prevention and Toxics (OPPT)
US Environmental Protection Agency
Washington, DC 20460

95 FEB 13 AM 8:13
RECEIVED

RE: TSCA Section 8(e) Notice

Dear Sir or Madam:

This notice is being submitted by to the Environmental Protection Agency (EPA) in accordance with the provisions of Section 8(e) of the Toxic Substances Control Act (TSCA), 15 USC § 2607 (e).

We are submitting results from a one year dog study with . This compound is being studied for research and development purposes and is currently in development as a pesticide.

claims the company name, the alpha-numeric designation, and the specific chemical identity of the substance at issue to be confidential business information (CBI). The chemical substance may be nonconfidentially identified as a "heterocycle".

was administered via admixture in the diet to Beagle dogs at levels of 0, 240, 1200, 12,000 and 30,000 ppm (5 dogs/sex/group) for 52 weeks. Respectively, these dietary levels were equivalent to doses of 8.41, 45.33, 498, and 1254 mg/kg/day for females and 8.56, 44.81, 453, and 1265 mg/kg/day for males. At 30,000 ppm, all male dogs were sacrificed after 26 weeks of treatment due to excessive toxicity as indicated by a significantly lower mean body weight gain, with 3 of 5 males exhibiting body weight loss (despite maximum food intake), and severe anemia. These dogs exhibited decreases in albumin, total protein, albumin/globulin ratio, and calcium and increases in platelet count, glutamic pyruvate transaminase activity, and alkaline phosphatase activity. All remaining dogs, including the 30,000 ppm females, survived to study termination.

Significantly lower body weight gains were observed in females at 12,000 and 30,000 ppm, but no effect on food consumption was observed for any group. In general, decreases in hemoglobin, red blood cell count, packed cell volume, albumin, total protein, albumin/globulin ratio, and calcium and increases in platelet count, glutamic pyruvate transaminase activity, and alkaline phosphatase activity were observed in females at 12,000 and 30,000 ppm. These findings, except for the decreases in the hematology

2/24/95

(2)

parameters, were noted also in males at 12,000 ppm. Statistically significant increases in 5' nucleotidase activity (measured at Weeks 26, 39, and 52) were observed in males and females at 12,000 ppm and females at 30,000 ppm. Statistically lower plasma urea was noted sporadically after Week 13, but a clear dose-response relationship was not apparent. Statistical differences were also noted at one or two time points for urinary pH and specific gravity without an apparent dose-response relationship. Statistically significant increases in absolute organ weights were observed for liver in males at 12,000 ppm and females at all levels, kidneys in males at 1200 and 12,000 ppm and females at 30,000 ppm, and thyroid in males at 12,000 ppm and females at 12,000 and 30,000 ppm. Histopathological examination, including 30,000 ppm males sacrificed after Week 26, revealed involution of the thymus and hepatocellular swelling at 12,000 and 30,000 ppm in both sexes. In addition, other changes in the liver included clumping and margination of cytoplasmic staining (centrilobular) in females at 12,000 and 30,000 ppm and males at 30,000 ppm, occasional vacuolated cells in females at 12,000 and 30,0000 ppm and centrilobular necrosis and fibrosis in males at 12,000 and 30,000 ppm. In the thyroid, hypertrophy of the follicular epithelium was observed in males at 12,000 ppm and males and females at 30,000 ppm. Prominent hemopoiesis was reported in the sternum or femur and joint of both sexes at 12,000 and 30,000 ppm and in the liver and spleen of males at 30,000 ppm. Histopathological changes in the testes and epididymides (reduced spermatogenesis in testes and absence of spermatids or round spermatids in epididymides) were also noted in males at 30,000 ppm, but these changes are most likely related to the overall poor condition of the animals at this level.

Based on slight changes in liver and kidney weights in the absence of any associated histopathological changes, the No Observed Adverse Effect Level (NOEL) in dogs is 1200 ppm or 45.07 mg/kg/day for both sexes.

SUPPORT INFORMATION OF CONFIDENTIALITY CLAIMS

1. Claims of confidentiality are being made on behalf of .

2. asserts this claim of confidentiality until such time as the chemical is approved for use in the United States. In the event that this chemical is never approved, asserts that the CBI information should be provided permanent protection. The structure and use of this chemical are unique. Disclosure of this information would provide our competitors with information on facets of our business that would be detrimental to our competitive position.

3. The information claimed as confidential has not been previously disclosed to any other governmental agency or to EPA.

4. This information has been disclosed to only a very limited number of investigators outside of who have performed either toxicity or efficacy testing. These individuals operate under a strict secrecy agreement. Any individuals who may work with this chemical will have all health/toxicology information disclosed to them as well, but only on the basis of strict secrecy and respect for the CBI nature of the information.

5. Any individuals to whom the CBI is revealed are warned of the nature of the information. Further, they are informed of their obligations to maintain secrecy should they terminate their employment with .

6. None of the information claimed as confidential appears in or is referred to in any advertising or promotional materials for the chemical or its end products, professional or trade publications, or any other media available to the public or to our competitors. Appropriate warnings do appear on safety data sheets, as considers that individuals who are requested

(3)

to work with these chemicals have every right to know as much about the chemical's toxicity as possible. Further, the information is only considered to be CBI with respect to the general public, insofar as our competitors could use the information in an unfairly competitive nature.

7. No previous confidentiality determinations have been made by EPA, other Federal agencies or courts in connection with this information.

8. believes that disclosure of this information to the general public would be likely to result in substantial harm to its competitive position. Disclosure of the **alpha numeric designation** and **chemical name** would provide some competitors with information about the specific chemistry of this area of our research and our business. Further, the type of toxicological testing being reported in the TSCA 8(e) notice would provide competitive information about the chemical's status in the research and development process and, therefore, the time remaining until commercialization. The **company name** is claimed as confidential because the particular chemical class being investigated is new to , and this information could influence decisions made by our competitors regarding the compounds they have in development.

9. A patent has not been issued for the specific chemical structure. However, the generic chemical structure is covered by a patent that is currently pending.

10. This chemical is not available commercially. It is in the earliest stages of research and development for pesticide use and may ultimately be developed into a commercial product.

11. We believe that disclosure of the chemical name would allow a competitor to synthesize the chemical. has invested a large amount of time and money into research of this particular chemical family, and information on specific chemical structures would harm our competitive position.

12. Disclosure of the chemical structure might reveal information on processes used to synthesize the compounds.

13. The CAS number is not known for this chemical.

14. Currently, this chemical is not the subject of FIFRA regulation or reporting.

Further questions regarding this submission may be directed to the undersigned at

Sincerely,

Director of Toxicology

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Glenn S. Simon, Ph.D., DABT
Director of Toxicology
Rhône-Poulenc
P.O. Box 12014
2 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 24 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and **refer to the reverse side of this page for "EPA Information Requests"** .

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure 13324A

Triage of 8(e) Submissions

Date sent to triage: _____

NON-CAP CAP

Submission number: 13324

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: 0 1 2 **pages** [illegible] **pages** 1,2,3

Notes:

Contractor reviewer : PDL **Date:** 4/21/95

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 0295 - 13324 (5) SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Confidential

SUB. DATE: 02/06/95 OTS DATE: 02/13/95 CSRAD DATE: 02/24/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER BENEFITS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME: Heterocycle

CAS# Confident

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
(0207)	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
(0215)	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
(0224)	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
(0248)	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

CTOX

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	YES	YES (DROP/REFER)	D06	(LOW) CARCINOGENICITY	R&D pesticide	
CAS SR	NO	NO (CONTINUE)		MED		
	(IN TRAMIN)	REFER		HIGH		

COMMENTS Non-CAP

#13324A
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Carcinogenicity is of low concern based on a 52-week feeding study in beagle dogs (5/sex/dose). Male dogs were fed for only 26 weeks due to excessive toxicity (body weight loss, anemia). Doses were 240, 1200, 12000 and 30000 ppm, which is equivalent to 8.41, 45.33, 498 and 1254 mg/kg/day for females, and 8.56, 44.81, 453 and 1265 mg/kg/day for males. No treatment-related tumors developed.